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Chapter 2

Alpha Amino Acid Metabolism as an Emerging Target in Cancer Stem Cells

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Abstract

Targeting the cancer stem cells can be a novel therapy to combat against proliferating cancer stem cells. Creating obstruction in metabolic pathways by inhibiting enzymes involved in metabolism can be a remarkable strategy to overcome the cancer progression. Development of inhibitor of transporter and various signalling pathways can also be helpful to eradicate growing tumour cells.

1. Introduction

The growing cancer cells have rarely cancer stem cells that have ability to divide indefinitely comprising a character of unipotency. The cancer stem cells (CSCs) has specified characters like heterogenous differentiation capacity, self-renewal, high metastatic potential, invasiveness, sphere forming potency and resistance to chemo/radiotherapy. Its population is small (0.001-0.1%) in whole tumour cell mass [1]. The CSCs use the altered metabolic pathway and cell cycle control mechanism to derive energy and rapid cancer cells proliferation respectively [2]. Thus, CSCs have ability to differentiate into tumour inducing cells (tics) and propagate as invasive tumour cells. For CSCs survival and maintenance, altered metabolism pathway eventually helps the CSCs to grow and undergo proliferation [3]. The CSCs possess high glycolytic phenotypic expression than mitochondrial respiration [2]. Apart from the these pathways, glutamine metabolism plays a crucial role in the survival and maintenance of the CSCs. Glutamine is a free α-amino acid, present in the body and its content is more in plasma

[4]. Glutamine regulate body nutrient metabolism, specially involved in the transportation of carbon, nitrogen and ATP molecules. It gives anabolic signals to enhance the protein synthesis in skeletal muscles. Its function is specific in different organs like liver, brain and pancreatic β-cells. In liver cells, it can act as a substrate for ureagenesis and can function in urea cycle metabolism. In brain, it removes ammonia and participates in glutamine metabolism. In pancreas, it is somehow linked to insulin secretion from the β-cells. In arterial blood and small intestine lumen, it generate antioxidant glutathione that eventually removes the reactive oxygen species (ROS) and do further regulation of cell signalling pathways [5]. Furthermore, glutamine acts as a substrate for biosynthesis of proline. Glutamine decomposition produces ammonia which is highly toxic to tissues and is unstable. To avoid this issue, there is precursor of glutamine that is α-ketoglutarate (AKG). AKG has property like solubility, stability, and non-toxic and can be transforming into glutamine by transamination reaction through glutamate dehydrogenase (GDH) enzyme [6]. Alteration in the glutamine/α-ketoglutarate pathway also helps in cell proliferation and induction of cancer. Overall, Tracing out the altered metabolic pathways can be one of the therapeutic strategies to target in cancer and cancer stem cells.

2. Metabolic Overview of Cancer Stem Cell

Otto Warburg traced out the clever mechanism that has been done by cancer proliferating cells. The presence of abundant oxygen in the cancer cell uses glucose molecules and produce lactate through glycolysis pathway [7]. Lactate as a fermentative product which yields more ATP than compared to oxidative phosphorylation. They also de-emphasise the mitochondrial oxidative phosphorylation. This whole mechanism is called Warburg effect [8]. Gaseous environment around a cell also plays an important role in maintenance of cells homeostasis. Outer region of tumour cells has abundance of oxygen and the inner cell mass comprises hypoxic condition (low O_2 levels) in order to regulate the expression of glucose transporter (GLUTs) and monocarboxylate transporter (lactate/pyruvate). These transporter transports glucose and lactate inside and outside of the cells respectively [7]. The CSCs also uses glutamine by some specific transporters in order to regulate the cancer cell proliferation [9]. It also influences the signalling pathways that help the CSCs to grow and proliferate. Low glucose uptake inside the CSCs directs mitochondrial respiration to become a source for ATP generation. CSCs also have specific cell surface markers such as $CD44_+$ in gastric/colon/ovarian cancer, $CD34_+/CD38_-$ in leukaemia cells, CD13/CD45/CD90 in hepatic cancer, CD117/CD90/EpCAM in pulmonary cancer, CD20/CD166/Nestin in melanoma cancer, $CD133_+/CXCR4_+$ and $CD24_+/CD44_+/ESA_+$ in pancreatic cancer and $CD44_+/CD24_-$ in breast cancer [10-13]. The most important CSCs markers that help in promoting cancer and invasiveness are CD44 [14]. So, targeting these pathways and markers can lead to combat against CSCs [15-17].

3. Metabolic Alterations and Regulation in Cancer Stem Cells

CSCs comprise noteworthy metabolism alteration and direct irregular gene expression. Recent studies revealed that there may be elevated glycolytic rate due to enhanced concentration of high glucose level. This elevation induces expression of certain genes (c-Myc, GLUT1, HK-1, HK-2 and PDK-1) which eventually help in glucose metabolism [3]. This event regulates growth of CSCs population inside a tumour. Inside a cancer cell, high PDK-1 levels facilitates TCA cycle entry and phosphorylate pyruvate dehydrogenase which supresses the conversion of pyruvate to acetyl coA [18]. Suppression of this step helps the pyruvate to convert into lactate in the cytosol which promotes cancer stem cells to derive energy. Some studies also revealed the elevated expression of HK-1 than HK-2. This may be due to HK-1 is comparatively much more involved in glycolytic metabolism. Increased levels of glucose uptake facilitate high levels of lactate production and ATP generation in cancer stem cells than non-cancer stem cells. Increased Akt signalling pathway also helps in survival of cancer stem cells [3]. Furthermore, several studies reported that B-cell lymphoma (Bcl-2) protein and its family members act as a metabolic regulator. Its metabolic role was confirmed by the presence of Bcl-2 associated death promoter (BAD) in complex with glucokinase [19]. The BAD aggregation along with glucokinase complex helps in cancer stem cells proliferation and biosynthesis [20-21].

4. Targeting Glycolysis and Mitochondrial Respiration

Cancer cells uses glycolytic pathway as an important source for energy production. So for therapeutic approach, we should target the enzymes that facilitate the metabolic pathway like GLUT 1-4, hexokinase, pyruvate kinase M2 and lactate dehydrogenase A [22-23]. Cancer stem cells have excellent ability to alter the metabolic pathway. The production of lactate makes the extracellular environment more acidic. Hypoxia-inducible factors (HIF) 1-α induces the expression of carbonic anhydrase which regulates the pH maintenance in the CSCs [24]. pH shift alters the drug target mechanism and HIF 1-α expression.

5. Glutamine Metabolism and Cancer

As we know that cancer cells uses glucose molecule as a metabolic source of energy, sidewise it also uses glutamine to grow rapidly and to synthesise new protein, nucleic acids and lipids [25]. Glutamine regulates the signalling pathways that help the cancer stem cells to grow and survival and metabolism through regulation of mitochondrial reactive oxygen species (ROS) [24]. It activate PI3K/Akt pathways that results in increased production of ROS. Glutamine is converted into glutamate by the action of glutaminase enzyme and the glutamate is converted into alpha-ketoglutarate by the action of glutamate dehydrogenase. The CSCs uses glutamine as a carbon source for rapid proliferation of cells. Cancer cells hires glutamine to provide substrates for TCA cycle. The oncogene c-Myc impacts glutamine metabolism by

stimulating the glutamine transporters like SLC5A1 and SLC7A1, promoting the glutaminase 1 expression by supressing the mi-RNA like miR-23A and miR-23B [26]. There are some glutamine analogue like DON (6-diazo-5-oxo-L-norleucine), acivicin and azoserine that shows anti-cancerous activities. DON inhibits glutamine metabolism and decreases the metastatic cancer. Blood glutamine levels can be decreased by histone deacetylase (HDAC) inhibitors such as phenylbutyrate to reduce proliferating cells in breast cancer. Some drugs also target the glutamine transporters such as IL-gamma-glutamyl-p-nitroanilide [24].
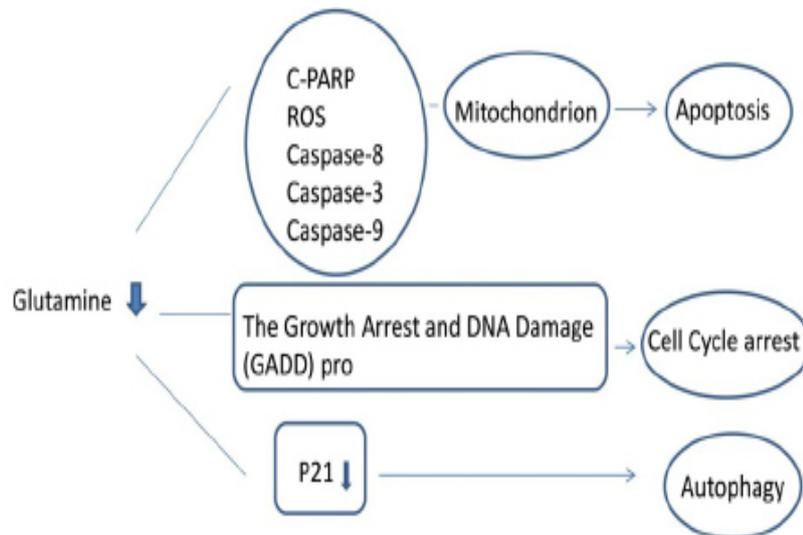

Figure 1: Involvement of alpha amino acid (glutamine) levels in the regulation of apoptosis, cell arrest and autophagy. Glutamine levels induce c-PARP, ROS, and caspase mediated apoptosis. Glutamine levels regulate cell cycle in GADD dependent manner. Decreased glutamine levels induce autophagy in the response of decreased p21 expression levels. C-PARP-cleaved PARP, GADD-Growth arrest and DNA damage-induced genes; ROS-reactive oxygen species

6. Glutamine-Alpha Ketoglutarate Metabolism

There are two well reported pathways related to conversion of glutamine to α-ketoglutarate. First pathway is known as glutaminolysis which facilitates breakdown of glutamine molecule by two deamination steps. In step first, glutamine is converted into glutamate and ammonia in the presence of enzyme glutaminase (GLS I). Glutaminase enzyme comprises two sub enzymes namely GLSI and GLSII [27]. These two enzymes are activated by pyruvate and phosphate [28]. Glutamate produced by phosphate activated glutaminase (PAG) reaction is reversely converted into alpha ketoglutarate either via glutamate dehydrogenase (GDH) in mitochondria or by transamination reaction. Glutamate in the presence of enzyme glutamine synthetase can be converted into glutamine, which can be used in metabolic regulation be the cell. The second pathway included glutaminase (GLS II) mediated that composed of glutaminase transaminase coupled to omega-amidase. Glutamine first converted to alpha keto acid that is alpha keto glutamate (KGM) in the presence of omega-amidase and then KGM is converted into alpha ketoglutarate and ammonia [29]. Now the conversion from glutamine to alpha ketoglutarate activate mTOR signaling which eventually plays a key factor in promoting cell growth and proliferation.
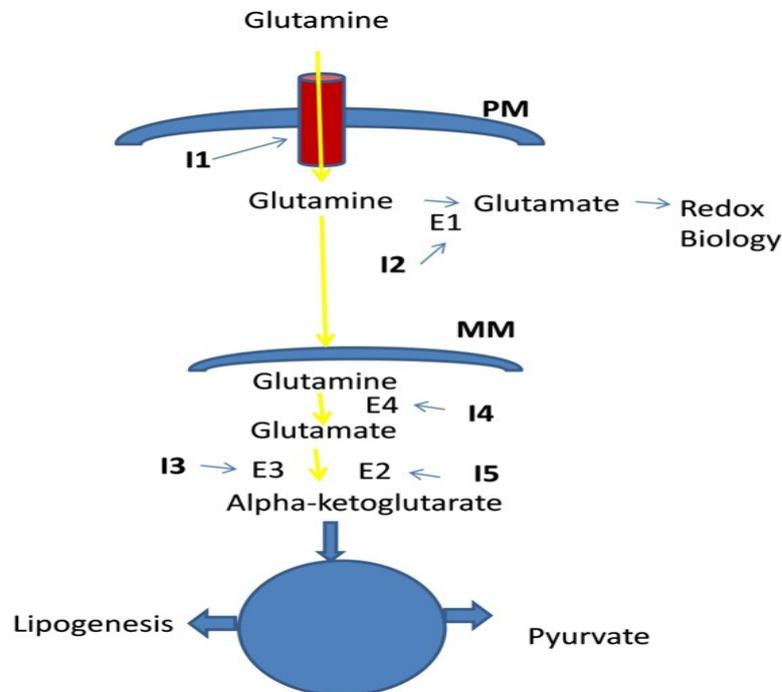
Figure 2: Enzyme targets and respective inhibitors of alpha amino acid (glutamine) metabolism. I1 inhibits the glutamine transporter. I1-GPNA (gamma-L-Glutamyl-p-nitroanilide); I2-Azaserine, Acivicin; I3-Aminooxyacetate; I4- Bis-2-(5-phenylacetamido-1,3,4-thiadiazol-2-yl)ethyl sulphide; I5- Epigallocatechin gallate; E1- gamma-glutamyl transferase.; E2-Glutamate dehydrogenase; E3-Transaminase; E4- gamma-glutamyl transferase; PM- Plasma membrane; MM- Mitochondrial membranex

7. Nutritional Fate of Glutamine-Alpha Ketoglutarate

7.1. Cell growth and proliferation

Once the glutaminolysis regulated the growth of cells by inducing mtor signaling pathways, mTORC1 assimilates outside and regulate intracellular signals to facilitate cell proliferation and growth [30]. Glutamine itself can act as a signal inducing molecule that eventually activate the mTOR signalling pathways, enabling the anabolic reaction and suppressing the catabolic reaction. Furthermore, increased level of alpha ketoglutarate stimulates the activation of mTORC1 signalling pathways with the help of leucine. It has been also observed that glutamine plays vital role in proliferation of intestinal cells by activating mitogen-activated protein kinases (MAPKs) and helps in proliferation of cancer cells [5].

7.2. Lipid metabolism

The adipocyte cells use glutamine carbon as an important substrate for lipid biosynthesis [31]. Triacylglycerol is synthesised from fatty acid derivatives from glutamine and stored in adipocyte tissue. Glutamine acts as a precursor molecule for lipid formation in body [5]. Unlike glutamine, dietary glutamine inhibits fat accumulation by increasing fatty acid oxidation or downregulating de novo lipogenesis; whereas non-glutamine containing diets increases body fats and hepatic triglycerides [32]. In addition to this, alpha ketoglutarate helps in formation of carnitine shuttle that helps the fatty acids to undergo β-oxidation in mitochondria and yields ATP molecules. Alpha ketoglutarate also plays a very crucial role in regulating the low-

density lipoproteins (LDL) and high-density lipoproteins (HDL) level and maintains their ratio and prevent the risk of hypercholesterolemia and lowering the risk of cardiac strokes [5].

7.3. Intestine structure and function

Glutamine plays a vital role in maintaining integrity and proper function of small intestinal mucosal cells by promoting mTOR signaling that eventually takes part in cell proliferation and growth, control apoptosis, protein turnover and do immunogenic functions [5]. Collaboration of glutamine and AKG play an important role in intestinal growth, function and its development [33].

7.4. Skeletal development

AKG mediated the synthesis of collagen fibres that helps in development of skeletal tissue. Moreover, it synthesise the proline and then hydroxyproline which are major component in collagen fibres that leads to development of skeletal muscle [5]. Moreover, studies revealed that AKG level rise may cause high glutamate synthesis and inducing the signalling pathways that controls bone metabolism. Studies also revealed that there are many antagonistic ionotropic receptors that inhibits bone formation, lowers the level of alkaline phosphate, reduces the calcium ion concentration and ultimately helps in reduction the proliferations of osteoprogenitors [34].

7.5. Cancer treatment

In cancer cells, along with consumption of glucose, it also consumes glutamine as metabolic substrates to get energy by metabolising it. It induces the mTOR signaling pathway that eventually leads the cancerous cell to grow and proliferate [5]. Furthermore, mTORC1 activity is highly up-regulated in cancerous cells [35]. The cancerous cells alters the metabolic pathways in order to survive and for proliferating itself at a faster rate. Glutaminolysis can be a major cause that helps the cancer cells to grow and proliferate via mTORC1 signalling pathways [36-37]. There are some glutamine analogs like acivicin, azaserine and 6-diazo-5-oxo-L-norleucine that can be used to prevent glutamine metabolism. Another drug, like gamma-L-lglutmyl-P-nitroanilide shows to inhibit ASCT2 transporters to dysregulate the glutamine uptake by cells, thus limiting the proliferation of cancer cells [38]. There are also two inhibitors of glutaminase (GLS) namely compound 968 and bis-2-(5-phenylacetamido-1, 2, 4-thiadiazol-2-yl) ethyl sulphide have potential to prevent cancer proliferation. Inhibition of glutamate dehydrogenase by epigallocatechin gallate decreases the proliferation of cancer cells by supressing its growth [5].

8. Tumour Regulatory Genes and Glutamine Metabolism

As we know the cancer cells are hungry to take the metabolite much rapidly other

than glucose molecule in order to fulfil its nutrient uptake that eventually helps in rapid proliferation of tumour cells [39]. There are some oncogenes and tumour suppressor genes that that regulate the metabolic pathways of glutamine which eventually helps in the proliferation and maintenance of redox balance in TCA cycle [40]. Activation of tumour suppressor gene namely p53 induces p21 that finally induces apoptosis and stops the proliferation of tumour cells [41]. p53 also regulates tumour suppression by inducing the expression of glutaminase2 (GLS2) that coverts glutamine to glutamate and ammonia [42]. Overexpression of this GLS2 helps in deduction of proliferating cancer cells in liver [43].

Another suppressor like sirtuins (SIRT) is NAD_+ dependent deacetylases that targets various types of proteins and amino acid sequence in nucleus, cytosol and mitochondria [44]. SIRT mainly respond to tissue under stress situation and damage DNA. SIRT4 inhibit glutamine dehydrogenase (GDH) that disables the cells to convert into glutamate to alpha ketoglutaric acid [45]. Targeting these factors can inhibit metabolism and helps in tumour suppression. mTORC1 also inhibits SIRT4 mechanically [39,46].

Another proto-oncogene, Myc also regulates growth and proliferation and helps in glucose metabolism [39]. It acts as a transcription factor that is deregulated in cancer cells. Any mutation or alteration in Myc gene leads to abnormal regulation and overexpression in uncontrolled cell proliferation and avoidance of apoptosis [47]. Studies revealed that Myc induces expression in glutaminase1 (GLS1) which is a key factor in cell proliferation and growth. Myc also helps in elevation of glutathione (GSH) levels that act as an antioxidant and helps to cancer cells to evade new tissues and promote malignancy [48]. Another oncogene namely K-RAS, play important role in metabolic transformation during tumour proliferation [49-50]. It is found that K-RAS transformation elevates glucose flux, decreases TCA cycle, and increases uptake of glutamine [51]. Any mutation in the K-RAS gene led to altered cellular signalling and metabolism. It inhibits glutamine dehydrogenase and activates aspartate transaminase via K-RAS regulated metabolic pathways [39].

9. Glutamine Transporters

Every tissue is a specific for the intracellular uptake of glutamine. Glutamine transporters facilitate and controls intake of certain amount of glutamine into it. There are two types of glutamine transporters namely sodium dependent transporter and sodium independent transporter [52]. Sodium dependent transporters comprises System A (alanine mediated), System N (nitrogenous group in side chain) and System ASC (amino-acid transporter-2 (ASCT2) transporters. In system A, there is a transporter named sodium-coupled neutral amino acid transporter 1 (SNAT1), plays vital role in uptake of glutamine in neuronal cells. Another transporter named SNAT2 plays crucial role in uptake of glutamine in adipose tissues. System N has the high affinity for glutamine and is marked by SNAT3 transporter that facilitates the release of

glutamine in astrocytes, skeletal muscle, periportal and perivenous hepatocytes, renal cells and transport glutamine in basolateral membrane [5]. The ASCT2 transport glutamine in skeletal muscles, adipocytes, epithelial cells and tumour cells. mTOR signaling regulates ASCT2 transporter and hampers cell growth and proliferation [53]. Sodium independent transporters include System L (leucine mediated) transporter. The glutamine transport via ASCT2 leads to leucine uptake by parallel leucine/glutamine antiport system which is mediated by L-type amino acid transporter1 (LAT1). Among these glutamine transporter LAT1 and LAT2 is most common. They believed to express in the intestine, adipose tissues and renal tissues [5].
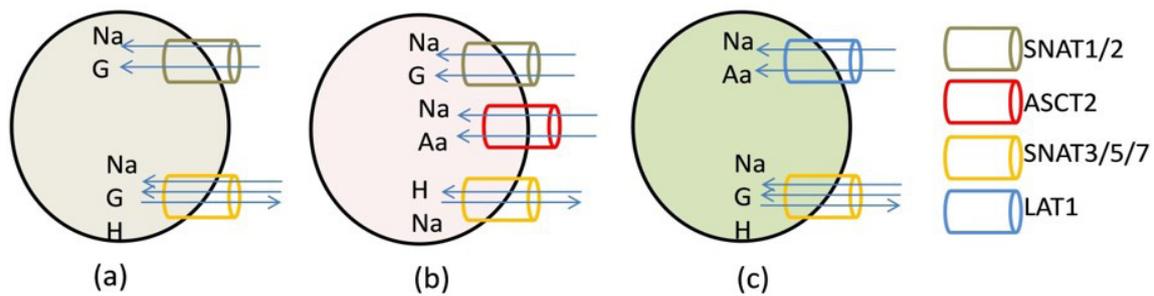
Figure 3: Different types of glutamine transporters and glutamine absorption mechanism in different tissues (a) Glutamine transporters and glutamine uptake by liver cells (b) Glutamine transporters and glutamine uptake by brain and other cells (c) Glutamine transporters and glutamine uptake by kidney tubule cells. Arrow shows the type of transport i.e. symport (same direction arrow), anti-port (opposite direction arrow). ASCT2-ASC amino acid transporter-2; LAT1-L-type amino acid transporter 1; SNAT-Sodium-coupled neutral amino acid transporter; Na-Sodium; G-Glutamine; H-Proton; Aa-Amino acid

10. Glutamine Induced Apoptosis: A Cancer Therapy Approach

In cancerous cell, both glucose and glutamine provides energy and facilitates continuous growth and proliferation. By targeting these of glucose and glutamine metabolism pathway, can control the growth and proliferation of cancer cells [54]. We can target certain enzymes and transporters of these pathways that dysregulate the whole process and helps in targeting via specific drugs to disable the growth and proliferation of cancer cells. This type of obstruction helps in inducing apoptosis or autophagy [55]. Glutamine can act as a precursor molecule for the biosynthesis of amino acids, proteins, and reduced molecules like NADH and helps in formation of anti-oxidant like glutathione and maintains redox homeostasis [56]. Cancer cells overcome apoptosis by inducing anti-apoptotic factors. This phenomenon can be important hallmarks of cancer [57]. Overexpression of these anti-apoptotic factors helps the cells to avoid death. Deprivation in the level of glutamine, restriction in glutamine uptake, decreasing the enzymatic activities, use of glutamine analogues and creating disturbances in metabolic pathways may be helpful to diminish the cell growth [57].

Glutamine deprivation introduces apoptosis via extrinsic or intrinsic pathways depending upon the nature of cell variety and condition [55]. In these situation, apoptosis have been reported in hepatoma, leukemia, myeloma and fibroblast tissues [55, 58-59]. Glutamine deprivation stimulates activation of caspases 2 and 3 that releases cytochrome c and enables apoptosis. The cells which have low amount of glutamine are more sensitive to Fas ligand

(CD95), TNF-alpha and heat shock mediated apoptosis [55]. Low level of glutamine induces low amount of glutathione, which acts as anti-oxidant. Glutathione is composed of gluta-mate, cysteine and glycine. This helps in maintaining the export and import of glutamate and cysteine residues respectively and acts as Xc-antiporter [54]. Decreased level of glutamine increases the ROS in mitochondria and induces apoptosis [60]. Apart from inducing apoptosis, the glutamine deprivation shows autophagy and cell cycle arrest in tumour cells by inducing p62 gene, growth arrest and DNA damage induced genes [61-62].

10.1. Glutamine Uptake Restriction

There are several transporters present in the membrane that helps in facilitating the glu-tamine uptake into the cells. In order to transport more glutamine inside the cell, the ASCT2 and LAT1 transporters is most likely up-regulated [63]. Drugs like tamoxifen, raloxifene and GPNA (gamma-L-glutamylp-nitroanilide has inhibitory effect on ASCT2 transporter (Table 1) [56][64]. LAT1 is inhibited by BCH (2-aminobicyclo-(2,2,1)-heptane-2-carboxylic acid) in cancer cells [65-66]. Restriction in glutamine supplementation inside the cancer cells can be a potent strategy for combating against cancers.

10.2. Inhibition of glutaminase

Inhibition of glutaminase (GLS) in cancer cells inhibited the cancer cell proliferation [67]. There are certain drugs like BPTES (bis-2-(5-phenylacetamido-1,2,4-thiadiazol-2-yl) ethyl sulphide 3) and compound 968 (5-(3-bromo-4-(dimethylamino)phenyl)-2,2-dimethyl-2-,3,5,6- tetrahydrobenzo[a]phenanthridin-4(IH)-one) shown excellent inhibitory effect on glu-taminase (Table 1) [68]. Glutaminase can also be inhibited by CB-839. Ebselen, chelerythrine, and apomorphine inhibit glutaminase activity in several studies [68-69].
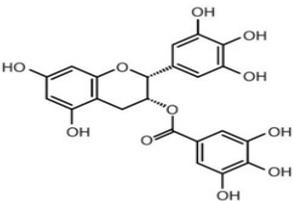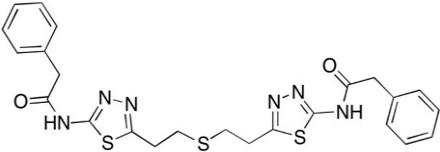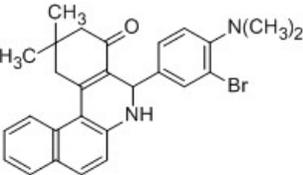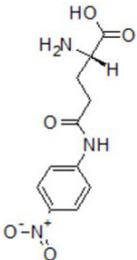
11. Targeting Drug Transporters

Cancer stem cells have high capacity of efflux system that disables the chemo-therapeu-tic drugs activity [14]. CSCs also express various Adenosine tri-phosphate-binding cassette (ABC) transporters such as ABCB1/P-gp/MDR1, ABCG2/BCRP/MXR and ABCB5 [70-71]. High ABCG2+ expression also seen in CSCs. Hypoxic conditions also induces the ABC trans-porters through transcription factor complex such as HIF1-α and HIF2-α [72-75]. Verapamil and valspodar are first generation inhibitors (FGI) to inhibit mitoxantrone efflux in leukaemia's cancer stem cells. High expression of ABCB1 transporter in leukaemia's cancer stem cells leads to development of chemo-resistant cells [76-77]. The second generation (SGI) drugs dexverapamil and valspodar showed high potency/specificity and low toxic level against these transporters in cancer cells [78]. These transporter showed interaction with these drugs and in-hibits cytochrome p-450. The third generation inhibitors (TGI) like Zosuquidar (LY3359) uses nano-molar concentration and have more potency against multi drug resistance (MDR) [79].
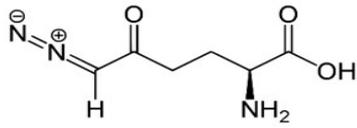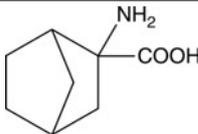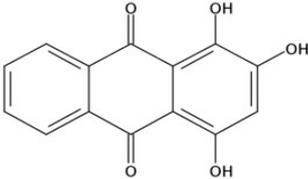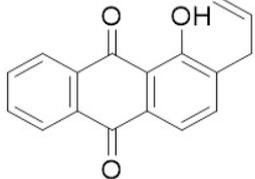
The fourth generation inhibitors (FGI) are the plant products that mainly include flavonoids or stilbenes [80]. Some natural products like cytarabin, trabectedin and halavan have been clinically approved due to their strong MDR reversal activity by impacting ABC drug transporters [81-84].

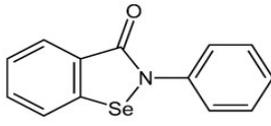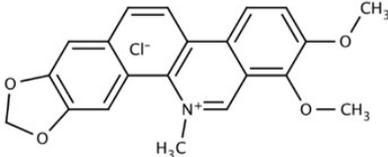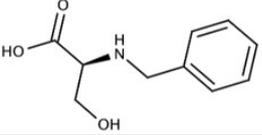## 12. Targeting Tumour Microenvironment

There are three basic parameters namely invasiveness, dormancy and chemo-resistant have been reported for their crucial help in CSCs progression [85]. The tumour microenvironment plays a vital role in cell proliferation through creating hypoxic conditions, regulating nutrition and low PH [86]. Microenvironment stimulates specific growth factors like vascular epithelial growth factors (VEGF) and fibroblast growth factors (FGF) that induces angiogenesis in the surrounding of cancer stem cells [87]. Growing tumour cells consumes much more oxygen and creates hypoxic condition. This situation is additionally regulated by hypoxia inducible transcription factors (HIF-1alpha/HIF-2alpha) [88]. Hence, targeting HIF1-α factor could be beneficial therapy for cancer stem cell treatment. During the stress and energy depletion stage of cell, mTOR activates the signalling pathways that promotes cancer stem cells to survive under stress microenvironment [35][89]. Acidic tumour microenvironment promotes invasiveness and regulates various genes that help in metastasis [90-91].

Table 1: Inhibitor and their glutamine metabolic targets in cancer cells

Compounds	Structure	Target	References
EGCG		GDH	[92]
BPTES		GLS1	[93]
Compound-968		Glutaminase C	[94]
GPNA		Glutamine transporter ASCT2	[64]

DON		Glutamine antagonist	[69]
BCH		Glutamine transporter SLC7A5	[65]
Purpurin		GDH	[95]
R162		GDH	[95]
Apomorphine		GLS1, GLS2	[96]
Ebselen		GLS1, GLS2	[96]
Chelerythrine		GLS1, GLS2	[96]
Benzylserine		Glutamine transporter ASCT2	[97]
Tamoxifen			
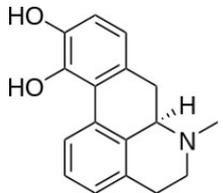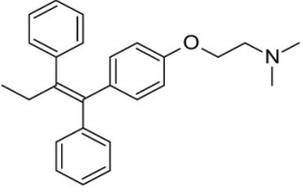
EGCG: Epigallocatechin gallate; GDH: Glutamate dehydrogenase; BPTES: Bis-2-(5-phenylacetamido-1,3,4-thiadiazol-2-yl)ethyl sulphide; GLS1: Glutaminase1; GAC=Glutaminase C; GPNA=L-γ-Glutamyl-p-nitroanilide; DON: 6-Diazo-5-oxo-L-norleucine; BCH: 2-aminobicyclo-(2,2,1)-heptane-2-carboxylic acid; GLS2: Glutaminase2

13. Acknowledgment

14. References

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